Appendix 1 (as supplied by the authors): Estimation of Asymptotic Case Fatality Rates using Competing Hazards During an Epidemic

We estimated asymptotic case fatality rates in our population using the approach described by Jewell and colleagues [1]. Consider an SIR model in a closed population, with initial population size $N(0) = S(0) + I(0)$. As illustrated in **Figure A1.1**, the disease induces death among those infected. As such, the distribution of infected individuals still infectious at some time x after infection arises from a competing risk framework.

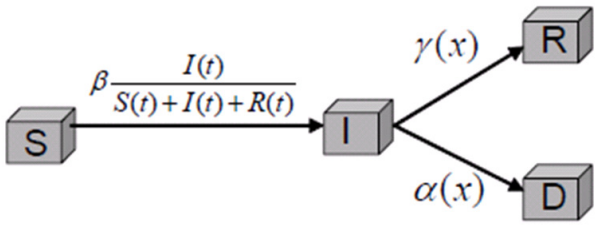

Figure A1.1. "SIR" model with mortality.
Boxes represent possible health states, with S = susceptible, I = infectious, R = recovered with immunity, and D = dead. Individuals move from the susceptible to infectious states at epidemic time = t at a rate defined by a transmission parameter (β) multiplied by the fraction of the population infected at t. Individuals recover and die at some time x after initial infection at rates of $\gamma(x)$ and $\alpha(x)$, respectively.

Let $\gamma(x)$ and $\alpha(x)$ be the type-specific hazard functions corresponding to "Recovery" and "Death", respectively. From competing-risks survival analysis [2], the proportion of infected individuals who survive the disease is

$$\varphi = \int_0^\infty \gamma(x) e^{-\int_0^\infty (\gamma(u)+\alpha(u))du} dx$$

In particular, if $\gamma(x) = \gamma$ and $\alpha(x) = \alpha$ then $\varphi = \gamma/(\gamma+\alpha)$. The quantity $1-\varphi$ is equivalent to the case-fatality rate. Using an ordinary differential equation model to represent a communicable disease[3](S = susceptibles, I = infectious individuals, R = recovered and immune, D = deaths, N = total population size):

$$\begin{cases} \frac{d}{dt}(S(t)+I(t)) = -(\gamma+\alpha)I(t) \\ \frac{dN}{dt} = -(1-\varphi)(\gamma+\alpha)I(t) \end{cases}$$

Appendix to Tuite AR, Greer AL, Whelan M, et al. Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *CMAJ* 2009. DOI:10.1503/cmaj.091807.

Where N(t) = S(t)+ I(t) + R(t) + D(t) :

$$N(0) - S(\infty) = (\alpha + \gamma)\int_0^\infty I(u)du \qquad \text{(A1.1)}$$

$$N(0) - N(\infty) = (1 - \varphi)(\alpha + \gamma)\int_0^\infty I(u)du \qquad \text{(A1.2)}$$

By dividing equation (A1.2) by equation (A1.1):

$$(1-\varphi) = (N(0)-N(\infty))/(N(0)-S(\infty)) \qquad \text{(A1.3)}$$

Therefore, the case fatality rate is related to the final size of the epidemic, and can be expressed as the ratio of *cumulative* deaths to *cumulative* infections. During the outbreak at any time *t*, I(t) > 0. For an arbitrary γ(x) and α(x), the proportion of recovered individuals is:

$$\varphi(t) = \int_0^\infty \gamma(x) e^{-\int_0^\infty (\gamma(u)+\alpha(u))du} dx$$

The proportion of deceased individuals is:

$$\omega(t) = \int_0^\infty \alpha(x) e^{-\int_0^\infty (\gamma(u)+\alpha(u))du} dx$$

The proportion of ever-infected individuals still in the infected class (I) at time *t* is:

$$1-\varphi(t)-\omega(t)$$

For the special case where hazards of recovery and death are constant:

$$\varphi(t) = \frac{\gamma}{\gamma + \alpha}\left(1 - e^{-(\alpha+\gamma)t}\right) \qquad \text{(A1.4)}$$

$$\omega(t) = \frac{\alpha}{\gamma + \alpha}\left(1 - e^{-(\alpha+\gamma)t}\right) \qquad \text{(A1.5)}$$

$$1-\varphi(t)-\omega(t) = e^{-(\alpha+\gamma)t} \qquad \text{(A1.6)}$$

We used equation (A1.5) to estimate asymptotic case fatality rates, with hazards for recovery and death derived from competing risks survival models [2].

To understand the importance of the method described here, recall the SARS experience: by the end of the outbreak, from worldwide data, it appeared that the case fatality rate was ~14%. However, the World Health Organization (WHO) had stated on April 13, 2003 that case fatality rates in Canada and in Hong Kong were 4.2% and 4.5%, respectively. By April 25–26, Washington Post calculated a SARS case fatality rate of 6% and stated that: "Although the rate of deaths from the strange new illness initially hovered as low as 3 percent, it has soared to twice as much in recent days." The National Post (Canada) also reported an increasing case fatality rate in Canada and called it the "sting of the SARS tail". On May 13, an Editorial in the Canadian Medical Association Journal quoted a 12.4% case fatality rate for Canada. By August, when the SARS outbreak was over in all parts of the world, the CFR were 17.5% in Canada and 17.0% in Hong Kong. At the time, this apparent increase resulted in concern that the virus was becoming more virulent with time. In reality, this effect derived from the use of cumulative case counts as a numerator, and cumulative deaths at a given point in time as the denominator for these calculations. However, the time interval from case onset to death was often substantial for SARS victims. Thus case counts (the denominator of the case fatality rate) increased rapidly early in the epidemic, with deaths (the numerator) requiring some time to catch up. This effect is illustrated graphically in **Figure A1.2.**

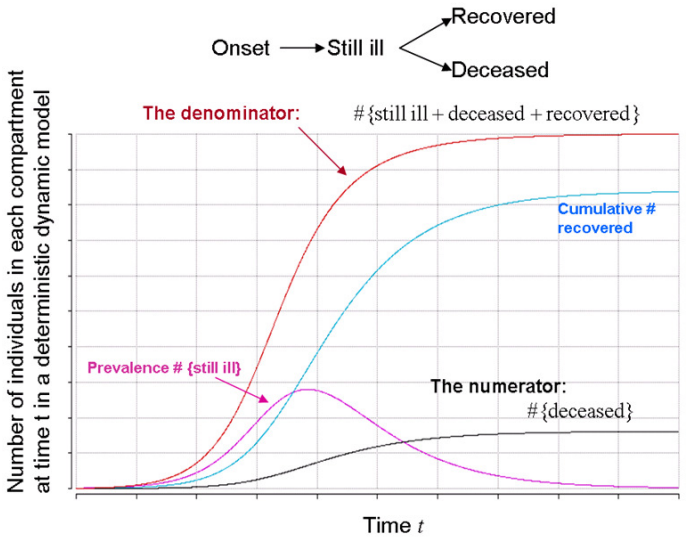

Figure A1.2. Schematic diagram illustrating the mechanistic basis for "rising case fatality rate" due to lags between disease onset and recovery or death.

References

1. NP Jewell, X Lei, AC Ghani, CA Donnelly, GM Leung, LM Ho, BJ Cowling, AJ Hedley: **Non-parametric estimation of the case fatality ratio with competing risks data: an application to Severe Acute Respiratory Syndrome (SARS)**. *Stat Med* 2007, **26**:1982–98.
2. TM Farley, MM Ali, E Slaymaker: **Competing approaches to analysis of failure times with competing risks**. *Stat Med* 2001, **20**:3601–10.
3. W Kermack, A McKendrick: **A contribution to the mathematical theory of epidemics**. *Proc R Soc Lond A* 1927, **115**:700–21.

